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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
06/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,865	BJORNSDOTTIR ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-82* is/are pending in the application.

4a) Of the above claim(s) *64,67 and 69-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-63,65,66 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/26/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-55 are cancelled.

Claims 56-82 are pending.

Claims 64, 67, and 69-82 are withdrawn from examination as detained in the Office Action.

Claims 55-63, 65, 66, and 68 are Examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of the invention of Group 1 (claims drawn to methods of diagnosing a psychiatric disorder), and the further election of the particular marker SG08S71, in the reply filed on 02/12/2008 is acknowledged. The traversal is on the ground(s) that in the examination of PCT/US04/30699 there were no unity of invention issues raised. This is not found persuasive because while the Examiner can not determine the examination methods of the international search authority that resulted in no establishment of a lack of unity of invention, Applicants argument does not point out any specific issue of the present Examiner's Lack of Unity finding (03/04/2008) making the requirement improper. Further, Applicants argue that the unifying concept relates to the discovery that the orientation of Inv8p23 is indicative of psychiatric disorder susceptibility, this argument is not found to be persuasive. For example, there is no requirement of the particular association with susceptibility in the methods of Group 3 drawn to predicting drug efficacy. Further, considering the kit of Group 2, while the association is recited in the independent claim (i.e. claim 70), the structural limitations are met by the cited prior art of Graw et al (2000). Finally,

Applicants have asserted that the requirement for restriction among the different particular recited markers is improper for the reasons previously presented. This is not persuasive because, as set forth in the Requirement of 03/04/2008 the different marker are structurally distinct as they are composed of different nucleotide sequences.

The requirement is still deemed proper and is therefore made FINAL.

Claims 64, 67, and 69-82 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention requiring non-elected markers (claims 64, 67, and 69) or distinct non-elected inventions (claims 70-82), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/12/2008.

Claim Objections

2. Claims 63, 66, and 68 are objected to for the specific recitation of non-elected subject matter in the alternative. In the Election of 02/12/2008 Applicants have elected for the examination of claims as they require the particular marker SG08S71. However the claims encompass numerous combinations other than the particularly elected single marker. It is noted that no claim is yet allowed. Upon allowance of a claim (either generic with regard to a surrogate marker, or the allowance of a claim specifically requiring the Elected marker), the propriety of the Requirement will be reconsidered, and if a generic claim is allowed the restriction requirement may be withdrawn, and if a claim specifically requiring the Elected marker is allowed, the restriction requirement

among different combinations requiring the allowed subcombination may be withdrawn (see MPEP 806.05(d)).

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 63, 66, and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63, 66, and 68 are unclear over recitation of the term 'SG08S71' (as consonant with the Election). The term does not appear to be an art recognized term to distinguish a particular nucleotide sequence, and the specification does not provide a limiting definition of what is required for the particular marker. Thus it is unclear what is required of the recited genetic marker. The claims may be made more clear if amended to require a particular nucleotide content in a particular nucleotide context identified using a sequence identifier (i.e.: SEQ ID NO:) from the Sequence Listing.

Claim Rejections - 35 USC § 112 1st ¶ - Written Description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 62, 65 and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed to the Written Description Training Materials revised March 25, 2008, available online at http://www.uspto.gov/web/menu/written.pdf.

Claims 62, 65 and 68 are drawn to methods wherein the orientation of Inv8p23 is determined by detecting any generic polymorphic site in linkage disequilibrium with Inv8p23 (claim 62) or surrogate marker in linkage disequilibrium with SG08S71 (as consonant with the Election). The claims thus encompass the detection of a wide variety of nucleotide contents in an enormous variety of nucleotide contexts which have the functional requirement of being indicative of a particular orientation of Inv8p23. In the case of the rejected claims, the specification does not provide the skilled artisan with an adequate written description of the required markers generically recited in the claims as in linkage disequilibrium with the Inv8p23 polymorphism or other recited markers.

The specification provides no limiting structures as to what nucleotide content of gene polymorphisms in a particular degree of linkage disequilibrium are required to estimate the Elected haplotype as required by the claims. Thus when the claims are analyzed in light of the specification, the claims encompass a large genus of nucleotide contents in a variety of sequence contexts.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant claims, the a priori identification of particular nucleotide content that is in linkage disequilibrium with Inv8p23, and thus may be indicative of its particular orientation, is critical to the claimed invention. However, given the particular recitations in the claims and the lack of limiting structural requirements of the required polymorphic sites, haplotypes, or surrogate markers in the specification, one of skill in the art can not a priori identify the required polymorphic sites, haplotypes, or surrogate markers in the breadth as generically encompassed by the claims that are diagnostically indicative of susceptibility to a psychiatric disorder. For example, while Fig 4 of the Drawings indicates a p-value of 2.61E-15 for linkage between the marker SG08S32 and the orientation at Inv8p23, Fig 6K indicates that there is not a significant association between the SG08S32 marker and bipolar disorder. The difficulty in identifying markers that are in linkage disequilibrium is demonstrated by Wall et al (2003), which teaches (p.587 - Linkage disequilibrium) that patterns of LD are well known for being noisy and unpredictable. For example, pairs of sites that are tens of kilobases apart might be in 'complete' LD, whereas nearby pairs of sites from the same region might be in weak LD.

Similarly, there can be tremendous differences in the extent of LD from one genomic region to another.

In conclusion, having considered the breadth of the claims, the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of (as consonant with the Election) methods requiring:

> Detection of a marker in linkage disequilibrium Inv8p23, wherein the marker is SG08S71, and wherein SG08S71 is detected by detecting the presence of either an A or G at position 501 of SEQ ID NO: 172.

does not does not provide an adequate written description of gene polymorphisms that are in linkage disequilibrium as required to estimate a haplotype.

Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

7. Claims 56-63, 65, 66, and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method of identifying a human subject as having an increased risk for developing panic disorder or panic disorder with bipolar disorder, comprising:
> obtaining a biological sample from said subject, said biological sample comprising nucleic acids from said subject; and
> detecting in said nucleic acids the presence of an A nucleotide at position 501 of SEQ ID NO: 172;
> wherein the presence of an A nucleotide at position 501 of SEQ ID NO: 17 is indicative of an increased risk for developing panic disorder or panic disorder with bipolar disorder.

does not reasonably provide enablement for diagnostic methods performed in non-human subjects, or methods for determining susceptibility to any other different psychiatric disorders or comorbid disorders, or the association with any other genetic content with any other different psychiatric disorders or comorbid disorders. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The instant claims are drawn to methods of diagnosing susceptibility to a psychiatric disorder or a comorbid disorder comprising detecting the orientation of the Inv8p23 genomic region.

The methods encompass the analysis of any subject organism, and encompass diagnosing susceptibility to any psychiatric disorder or a comorbid disorder.

The claims encompass methods of detecting the orientation of the Inv8p23 region comprising analysis of any markers in any level of linkage disequilibrium with Inv8p23 or the SG08S71 markers (as consonant with the Election).

The claims encompass detection of any nucleotide content that is the SG08S71 markers (as consonant with the Election).

Direction provided by the specification and working example

The instant specification provides an analysis of the orientation of the Inv8p23 genomic region as determined by FISH experiments (p.41-42), and asserts a p-value of 0.07 in the association of the inverted phenotype in panic disorder (PD) subjects as compared to controls.

The specification further teaches that because FISH is not an ideal method for the study of large patient sets, surrogate markers for the orientation of the 8p23 genomic region were identified and used for analysis. The specification does not teach

any surrogate makers that are completely indicative of 8p23 orientation, and provides that the G allele of the SG08S5 has a frequency of 91.3% in inverted chromosomes, and 9.8% in the common orientation (p.43).

With regard to the elected marker SG08S71, the specification provides the marker is an A/G biallelic SNP at position 501 of SEQ ID NO: 172 (p.75-76) and that the A allele of the marker is significantly associated with increased risk of PD (Figs 5A and 11C8)and PD with the particular comorbid disorder bipolar disorder (BPD) (Fig 6K), but not with BDP without PD (Figs 7K and 11E8).

The specification does not provide any analyses of any non-human subjects.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of any particular nucleotide sequence is high, the unpredictability with regard to the association of any nucleotide content with a particular phenotype is even higher. The unpredictability is demonstrated by the prior art and the post-filing art, and the instant specification.

Because the claims encompass diagnostic methods in any subject organism, whereas the specification provides only an analysis of human subjects, it is relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, form organism to any other different organism. Such unpredictability in interspecies extrapolation is addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

Because the claims are drawn to methods that encompass the detection of any polymorphisms to in any level of disequilibrium with the Inv8p23 orientation or the elected SG08S71, as well as associations with any psychiatric disorder or comorbid disorder, whereas the specification teaches only the significant association of particular SNP content with particular phenotpyes (i.e. an A nucleotide at position 501 of SEQ ID NO: 17 is indicative of an increased risk for developing panic disorder or panic disorder with bipolar disorder), it is relevant to point out the unpredictability in associating any genetic variation with a particular phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627).

Given the breadth of the claims as encompassing any polymorphisms in any level of linkage disequilibrium to estimate any haplotype, it is relevant to point out the unpredictability in associating any particular gene mutation with a particular phenotype. This is particularly true where the instant claims encompass sensitivity to any drug and any side effects to any drug. As evidence of the unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be

included in the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

The instant specification indicates the unpredictability associated with the breadth of the claims. For Example, p.41-43 of the specification provide the only actual analysis of direct observation of Inve8p23 observation, where the inverted allele is not significantly associated with PD (i.e. p=0.07 is not significant). Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion). And with regard to makers asserted to be indicative of 8p23 orientation and their use in the claimed methods, while Fig. 4 indicates that the marker DG8S170 is significantly associated with 8p23 orientation, Fig 5D indicates that the marker is not significantly associated with PD. And while Fig. 4 indicates that the marker SG08S32 is significantly associated with 8p23 orientation, Fig

6K indicates that the marker is not significantly associated with PD with BDP and Fig 7J indicates that the marker is not associated with BPD without PD. Similarly, with regard to the Elected SG08S71 marker, Fig 7K indicates that the marker is not significantly associated with BPD without PD.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Such experimentation would include large case:control studies in multiple populations of any subject organism of interest to demonstrate a reliable association of the Inv8p23 orientation, or any marker in any level of disequilibrium with Inv8p23, with susceptibility to any psychiatric disorder or any comorbid disorder. One would have to perform large case:control studies to establish whether or not any associations are reliable and robust. Such experimentation would be extensive, especially considering in the lack of data presented in the instant specification regarding statistically significant associations between Inv8p23, or a multitude of markers asserted by the specification to be surrogates for Inv8p23 orientation, and several psychiatric disorders analyzed in the specification. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of genetic content and phenotype, beyond those identified in the specification as set forth in this rejection (i.e. an A nucleotide at position 501 of SEQ ID NO: 17 is indicative of an increased risk for developing panic disorder or panic disorder with bipolar disorder) would be identified.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope as encompassed by the claims.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 56-61 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15 and 16 of copending Application No. 11/663,231. Both Applications are commonly assigned to deCode Genetics Ehf. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the claims of the conflicting application are drawn to methods of diagnosing susceptibility to psychiatric disorders or comorbid disorders where the orientation of Inv8p23 is used to diagnose the phenotype.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634